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PCS10915AJR-PROV

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2 AUG 2000

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Request for grant of a Patent

Form 1/77

Patents Act 1977

1 Title of invention

1 Please give the title of the invention

PARTICULATE COMPOSITION

2 Applicant's details

☐ **First or only applicant**

2a If you are applying as a corporate body please give:

Corporate name
PFIZER LIMITED

Country *(and State of incorporation, if appropriate)*
UNITED KINGDOM

2b If you are applying as an individual or one of a partnership please give in full:

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Forenames

2c **In all cases,** please give the following details:

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RAMSGATE ROAD
SANDWICH
KENT

6892673001

UK postcode CT13 9NJ
(if applicable)

Country UNITED KINGDOM

ADP number
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2d, 2e and 2f:
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Second applicant (if any)

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3
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⬇ *Please give details below*

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Agent's address
PFIZER LIMITED
RAMSGATE ROAD
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6296446001

Agent's ADP number

3b:
If you have appointed an agent, all correspondence concerning your application will be sent to the agent's United Kingdom address.

3b If you have not appointed an agent please give a name and address in the United Kingdom to which all correspondence will be sent:

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4 Reference number

4 Agent's or applicant's reference number *(if applicable)* PCS10915AJR-PROV

5 Claiming an earlier application date

5 Are you claiming that this application be treated as having been filed on the date of filing of an earlier application?

Please mark correct box

Yes ☐ No ☒ ➡ *go to 6*

⬇ *please give details below*

❑ number of earlier application or patent number

❑ filing date *(day month year)*

❑ and the Section of the Patents Act 1977 under which you are claiming:

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15(4) (Divisional) ☐ 8(3) ☐ 12(6) ☐ 37(4) ☐

6 Declaration of priority

6

If you are declaring priority from a PCT Application please enter 'PCT' as the country and enter the country code (for example, GB) as part of the application number.

Please give the date in all number format, for example, 31/05/90 for 31 May 1990.

6 If you are declaring priority from previous application(s), please give:

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7 Inventorship

7 Are you (the applicant or applicants) the sole inventor or the joint inventors?

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A statement of Inventorship on Patents Form 7/77 will need to be filed (see Rule 15).

8

Please supply duplicates of claim(s), abstract, description and drawing(s).

8 Checklist

8a Please fill in the number of sheets for each of the following types of document contained in this application.

Continuation sheets for this Patents Form 1/77 [ ]

Claim(s) [4] Description [14]

Abstract [ ] Drawing(s) [ ]

8b Which of the following documents also accompanies the application?

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Priority documents *(please state how many)* [ ]

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PARTICULATE COMPOSITION

This invention relates to a particulate composition containing eletriptan, or a pharmaceutically acceptable salt thereof, which is capable of achieving a sigmoidal pattern of controlled drug release and to processes for the preparation of, pharmaceutical formulations containing and the uses of such a composition.

Eletriptan, 3-{[1-methylpyrrolidin-2(R)-yl]methyl}-5-(2-phenylsulfonylethyl)-1H-indole, is disclosed in WO-A-92/06973. A preferred hydrobromide salt of eletriptan is disclosed in WO-A-96/06842 and a pharmaceutical formulation comprising eletriptan hemisulphate and caffeine is disclosed in WO-A-99/01135.

Eletriptan is a 5-$HT_{1B/1D}$ receptor agonist and has been shown to be highly effective in the treatment of migraine. More recently, the use of eletriptan in the prevention of migraine recurrence has been disclosed in WO-A-00/06161. Migraine recurrence is a separate condition from migraine itself and can be defined as the return of a moderate or severe migraine headache within 24 hours of the first dosing with medication.

In certain instances, it is useful to administer eletriptan to a patient in a controlled way over a period of time. In the preventative treatment of migraine recurrence, for example, it is useful to achieve a delayed and/or sustained release of eletriptan that will protect the patient from the return of a moderate or severe migraine headache within a 24 hour period from initial dosing of drug. Accordingly, it is an object of this invention to provide a well-tolerated pharmaceutical composition of eletriptan, or a pharmaceutically acceptable salt thereof, suitable for oral administration, that will release eletriptan in the gastrointestinal tract of a patient, after an initial delay and/or over a sustained period of time, in a sigmoidal fashion. Since in those patients susceptible to migraine recurrence it will be more convenient to administer sufficient eletriptan by a means to both treat an initial migraine attack and to prevent migraine recurrence, it is a further object of the present invention to provide a

dual release pharmaceutical formulation of eletriptan, or a pharmaceutically acceptable salt thereof, containing both sigmoidal type controlled-release and immediate-release forms of the drug.

In order to achieve an oral, controlled release formulation of a drug, capable of achieving a sigmoidal release, comprising a core of the drug coated with a water-insoluble, polymeric membrane, the drug selected must have certain properties. In particular, its aqueous solubility and dissolution characteristics must be such that it both dissolves adequately at the membrane-drug interface and passes at a suitable rate through the membrane when the formulation is hydrated in the gastrointestinal tract, properties that are extremely difficult, if not impossible to predict or determine in isolation. The idiosyncratic properties of different drugs and their individual salt forms has prevented the general applicability of such technology and made it impossible to predict whether or not a given drug in a given form can be delivered in a sigmoidal controlled release manner. In any event, it is believed that the utility of such controlled-release technology may be restricted to certain highly water-soluble drugs such as diltiazem hydrochloride (see *Journal of Controlled Release*, 1997, **44**, 263-270).

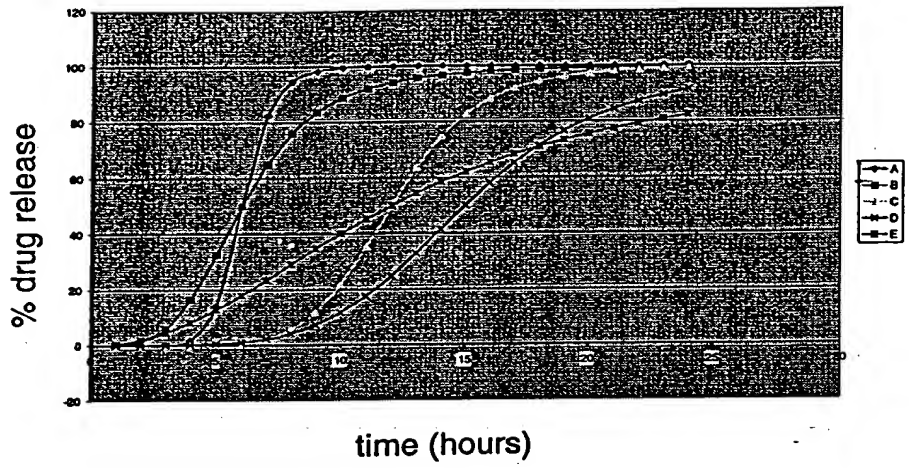
Several salts of eletriptan have been identified that have properties which make them particularly suitable for development as drug substances. These include the hydrobromide salt which has low aqueous solubility (4 mg/ml at 20 °C) similar to eletriptan free base (2.5 mg/ml at 20 °C), and the hemisulphate salt which has high aqueous solubility (>200 mg/ml at 20°C). It is therefore desirable to provide a controlled release formulation capable of achieving a sigmoidal pattern of drug release and suitable for oral administration that is equally useful for the delivery of any form of eletriptan, regardless of its solubility. It has now been unexpectedly and advantageously found that when eletriptan or a pharmaceutically acceptable salt thereof is formulated as a core of drug, coated with a certain water-insoluble, polymeric membrane, such a formulation is capable of achieving a sigmoidal pattern of controlled drug release when administered orally, in spite of the unpredictability of such

technology and the variable, sometimes low solubility of the different salt forms.

Accordingly, the invention provides a pharmaceutical composition in particulate form, suitable for oral administration, including a core containing eletriptan or a pharmaceutically acceptable salt thereof, the core being coated with a water-insoluble, permeable coating including one or more acrylic copolymer(s) containing trimethylammoniumethylmethacrylate groups, said composition being capable of achieving a sigmoidal pattern of controlled drug release.

The term 'controlled drug release' means control of the rate of dissolution of the drug in a body fluid (e.g. in the gastrointestinal tract) such that it is slower than the intrinsic dissolution rate of the drug in such a medium. It may otherwise or additionally mean a delayed release of drug. In all these cases, such controlled release is brought about by the nature of the drug's formulation. This effect results in the drug being released into solution over a longer period than would be achieved if the drug was administered without control of its release pattern and/or after an initial delay. The pattern of controlled drug release achieved by the present formulation is known as sigmoidal, i.e. a release profile exhibiting (a) an optional lag time from administration during which no drug or very little drug (e.g. less than 5% by weight) is released, followed by (b) a phase where the rate of drug release increases, followed by (c) a phase where the rate of drug release decreases towards zero as the amount of drug in the formulation is exhausted. The changeover from phase (b) to phase (c) usually occurs when at least 50% by weight of the drug has been released. Specific examples of sigmoidal controlled drug release profiles are shown in Example 3, for Examples of the present invention. Other patterns of sigmoidal controlled drug release are illustrated below.

Sigmoidal release



In a further aspect, the invention provides a particulate composition, as defined above, for use as a medicament.

In a further aspect, the invention provides the use of a particulate composition as defined above in the manufacture of a medicament for (a) the treatment of a disease for which a 5-$HT_{1B/1D}$ receptor agonist is indicated, (b) the treatment of migraine or (c) the prevention of migraine recurrence.

In a further aspect, the invention provides a method of (a) treatment of a disease for which a 5-$HT_{1B/1D}$ receptor agonist is indicated, (b) treatment of migraine or (c) prevention of migraine recurrence in a mammal, including a human, comprising administering to said mammal a therapeutically effective amount of a particulate composition as defined above.

The pharmaceutically acceptable salts of eletriptan include the acid addition salts thereof. Suitable acid addition salts are formed from acids which form non-toxic salts and examples are the hydrochloride, hydrobromide, hydroiodide, sulphate, hemisulphate, nitrate, phosphate, hydrogenphosphate, acetate, maleate, fumarate, lactate, tartrate, citrate, gluconate, succinate,

saccharate, benzoate, methanesulphonate, ethanesulphonate, benzenesulphonate, para-toluenesulphonate and pamoate salts.

Preferred acid addition salts of eletriptan for use in the present invention are the hydrobromide and hemisulphate.

A pharmaceutically acceptable acid addition salt of eletriptan may be readily prepared by mixing together solutions of eletriptan and the desired acid. The salt may precipitate from solution and be collected by filtration or may be recovered by evaporation of the solvent.

Also included within the scope of the present invention are polymorphs and solvates (including hydrates) of eletriptan or a pharmaceutically acceptable salt thereof.

The core of the particulate composition, which preferably does not contain an organic acid, may be constituted in several ways. For example, in one embodiment, eletriptan, or a pharmaceutically acceptable salt thereof, is optionally combined with one or more pharmaceutically acceptable extrusion aid(s) (e.g. a microcrystalline cellulose, a microcrystalline collagen, an amylose, pregelled starch, bentonite, a pharmaceutically acceptable clay such as kaolin), binder(s) (e.g. a polyvinyl pyrrolidone, a copolymers of vinyl pyrrolidone/vinyl acetate, a hydroxypropyl methylcellulose, sodium carboxymethylcellulose) or diluent(s) (e.g. lactose, mannitol, sucrose) and formed into particles suitable for coating (for instance, by extrusion spheronisation, direct pellitisation/high shear granulation, fluid bed granulation or spray drying/melt congealing) to form the drug core. In another embodiment, a solution (in a suitable solvent such as water or a mixture of water and ethanol) or mixture of eletriptan, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable binder (e.g. a hydroxypropyl methylcellulose, a hydroxypropyl cellulose, acacia, carboxymethylcellulose sodium, dextrin, ethylcellulose, gelatin, glucose, guar gum, hydroxyethyl cellulose, methylcellulose, a polymethacrylate, a polyvinyl pyrrolidone, pregelatinised starch, sodium alginate, zein) is layered onto the surface of a

pharmaceutically acceptable seed, typically a particle (e.g. a sphere) of sucrose, starch, microcrystalline cellulose or any combination thereof, to form the drug core. Such layering may be by solution layering or powder layering. The embodiment preferred will depend on the particular form of drug used. For example, with drug forms which have adequate solubility in suitable solvents, such as eletriptan hemisulphate, layering a solution of the drug onto a pharmaceutically acceptable seed may be preferred.

The core typically has a width or diameter of from 0.2 to 2 mm, preferably of from 0.5 to 1.4 mm. The amount of eletriptan present in the core will typically be from 10 to 90% by weight, preferably from 20 to 60% by weight.

In order to provide a smooth surface to the core, or to prevent attrition of the core during later stages of manufacture, an additional protective layer, typically composed of hydroxypropyl methylcellulose, hydroxypropyl cellulose, poly(vinyl alcohol), another hydrophilic polymer, or any mixture thereof, may be inserted between the core and the water-insoluble, permeable coating. Typically, protective coating levels will vary from 1 to 10% by weight.

The term 'water-insoluble, permeable coating' used in the definition of the particulate composition above means a coating which is resistant to degradation under the aqueous conditions encountered in the gastrointestinal tract for at least 24 hours but which is permeable to the drug when in contact with an aqueous medium so as to allow the passage of dissolved drug through the coating. The coating thickness is typically from 10 to 100 microns, preferably from 20 to 50 or from 40 to 80 microns.

The acrylic copolymer(s) containing trimethylammoniumethylmethacrylate groups included in the water-insoluble, permeable coating is/are preferably selected from the Eudragit RL (Trade Mark) and Eudragit RS (Trade Mark) copolymers manufactured by Röhm Pharma GmbH. These copolymers contain chloride counter-ions, which are preferred counter-ions for the present invention. A ratio of about 95:5, by weight, Eudragit RS (Trade Mark):Eudragit RL (Trade Mark) is particularly preferred.

The water-insoluble, permeable coating may include one or more additional substances other than an acrylic copolymer containing trimethylammoniumethylmethacrylate groups, such as a plasticiser (e.g. an acetylated monoglyceride, triethylcitrate, acetyltriethyl citrate, tributyl citrate, acetyltributyl citrate, other citrate esters, dibutyl phthalate, diethyl phthalate, another phthalate ester, diethyl sebacate, dibutyl sebacate, diethyl fumarate, diethyl succinate, a polyethylene glycol, glycerol, sesame oil, a lanolin alcohol, triacetin), an anti-tacking agent (e.g. talc, calcium stearate, colloidal silicon dioxide, glycerin, magnesium stearate, mineral oil, a polyethylene glycol, zinc stearate, aluminium stearate, glycerol monostearate), a wetting agent (e.g. sodium lauryl sulphate, stearyl alcohol, acacia, benzalkonium chloride, cetomacrogol emulsifying wax, cetostearyl alcohol, cetyl alcohol, cholesterol, diethanolamine, sodium stearate, glycerol monostearate, hydroxypropylcellulose, a lanolin alcohol, triethanolamine, lecithin, poloxamer, a polyoxyethylene alkyl ether, a sorbitan ester, a stearyl alcohol, simethicone) or a water insoluble polymer (e.g. ethylcellulose, cellulose acetate, a polymethacrylate copolymer). When used, the preferred plasticiser is triethylcitrate, the preferred anti-tacking agent is talc and the preferred wetting agent is sodium lauryl sulphate. The amount of plasticiser used is preferably from 0-30% by weight compared with the amount of acrylic copolymer used and is most preferably about 20%. The amount of anti-tacking agent used is preferably from 0-150% by weight compared with the amount of acrylic copolymer used and is most preferably 50-100%. The amount of wetting agent used is preferably from 0-5% by weight compared with the amount of acrylic copolymer used.

The particulate composition may be further coated with a hydrophilic polymer to provide a smooth surface, to prevent attrition of during later stages of manufacture or to colour the bead. The further coating is typically composed of hydroxypropyl methylcellulose, hydroxypropyl cellulose, poly(vinylalcohol) or any combination thereof and may also contain dyes or pigments. When present this further coat will typically account for from 1 to 10% by weight of the final product.

The preferred profile of sigmoidal drug release according to the present invention can be defined by the following ranges, which refer to the amount of drug released into a phosphate buffer of pH 7.5 (see the European Pharmacopeia for preparation), containing sodium chloride at a concentration of 0.1 mol/l. The profiles were measured using a dissolution apparatus type 1 (baskets) according to USP XXIII, at 100 rpm and 37 °C.

Amount drug released (% by weight)	Time (hours)
5	1.5-7.0
50	4.0-11.0
95	6.5-20

Thus in a further aspect, the invention provides a pharmaceutical composition capable of delivering eletriptan, or a pharmaceutically acceptable salt thereof, into an aqueous solution buffered at pH 7.5 with a sigmoidal controlled release profile wherein (a) 5% by weight of the drug is released at a time point from 1.5 to 7 hours following addition to the aqueous solution, (b) 50% by weight of the drug is released at a time point from 4 to 11 hours following addition to the aqueous solution and (c) 95% by weight of the drug is released at a time point from 6.5 to 20 hours following addition to the aqueous solution.

Such a particulate composition for achieving a sigmoidal pattern of controlled drug release, as described above, may be combined with a composition of the drug that achieves an immediate release to provide a dual release formulation. The overall release of drug from such a dual release formulation in the gastrointestinal tract will then be characterised by (a) a rapid release of drug on administration of the dosage form that quickly peaks and falls back to near zero (b) an optional lag time during which no drug or very little drug is released (c) a phase where the rate of drug release increases again and (c) a phase where the rate of drug release decreases towards zero as the amount of drug in the formulation is exhausted. Phase (a) can be attributed to the

immediate release composition and phases (b)-(d) to the sigmoidal controlled release composition. Such a dual release formulation is particularly useful in treating a patient for both migraine and the prevention of migraine recurrence with a single dose of drug.

Thus in a further aspect, the invention provides a dual release formulation which comprises a sigmoidal controlled release particulate composition of eletriptan, or a pharmaceutically acceptable salt thereof, as defined above, in combination with an immediate release composition of eletriptan, or a pharmaceutically acceptable salt thereof.

In a further aspect, the invention provides the use of dual release formulation as defined above in the manufacture of a medicament for the treatment of migraine and the prevention of migraine recurrence.

In a further aspect, the invention provides a method of treatment of migraine and the prevention of migraine recurrence in a mammal, including a human, comprising administering to said mammal an effective amount of a dual release formulation as defined above.

A composition that would achieve a more immediate release of eletriptan is the core of the particulate composition described above alone, i.e. without the water-insoluble permeable coating, optionally additionally comprising a disintegrant such as sodium cross-linked carboxymethylcellulose.

Different particulate compositions according to the invention may also be mixed together to provide formulations with composite release profiles which in certain cases may be zero order.

A particulate composition of the invention can be administered alone or in admixture with a suitable pharmaceutical excipient, diluent or carrier selected with regard to the intended route of administration and standard pharmaceutical practice.

Thus in a further aspect, the invention provides a pharmaceutical formulation including a particulate composition of the invention and one or more pharmaceutically acceptable excipient(s), diluent(s) or carrier(s).

A particulate formulation of the invention is preferably administered orally in the form of tablets, capsules or ovules, which may contain flavouring or colouring agents.

Such tablets may contain excipients such as microcrystalline cellulose, lactose, sodium citrate, calcium carbonate, dibasic calcium phosphate and glycine, disintegrants such as starch (preferably corn, potato or tapioca starch), sodium starch glycollate, croscarmellose sodium and certain complex silicates, and granulation binders such as polyvinylpyrrolidone, hydroxypropylmethylcellulose (HPMC), hydroxypropylcellulose (HPC), sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, stearic acid, glyceryl behenate and talc may be included.

Such capsules may be made of hard or soft gelatine and contain excipients such as lactose, starch, a cellulose, milk sugar or a high molecular weight polyethylene glycol.

The particulate compositions of the invention are most preferably administered contained in hard gelatine capsules.

The daily dosage level of eletriptan or a pharmaceutically acceptable salt thereof will usually be from 1 to 4 mg/kg (in single or divided doses).

Thus tablets or capsules comprising the particulate formulations of the invention may contain from 20 to 240 mg of eletriptan or a pharmaceutically acceptable salt thereof for administration singly or two or more at a time, as appropriate. The physician will in any event determine the actual dosage which will be most suitable for any individual patent. The above dosages are exemplary of the average case. There can, of course, be individual instances

where higher or lower dosage ranges are merited and such are within the scope of this invention.

The particulate compositions of the invention can also be administered in combination with a prokinetic or antiemetic agent.

It is to be understood that all references herein to treatment include curative, palliative and prophylactic treatment.

The following Examples illustrate the invention.

Example 1: Particulate composition containing eletriptan hydrobromide

Preparation of drug-containing core:

A dry blend is made up by mixing 1455.0g eletriptan hydrobromide, 773.0g of microcrystalline cellulose (Avicel PH101) and 773.0g lactose in a planetary mixer (EG20, Peerless). Purified water (1400g) is added to give a wet mass that is subsequently extruded using a 1.0 mm screen (Nica extruder E140, Aeromatic Fielder). The extrudates are rounded in a spheroniser (Caleva Model 15) and thoroughly dried in a fan-assisted oven at 50 °C for 12 hours. The extrudates have the following approximate size distribution, referring to their diameter: <0.71mm, 8% (by weight); 0.71-1.18mm, 89.5% (by weight); 1.18-1.4mm, 2% (by weight); >1.4mm, 0.5% (by weight). The 0.71-1.18mm fraction is used in the subsequent coating step.

Preparation of coating dispersion

A coating dispersion is made in the following manner. In a container equipped with a mixer, 20.0g talc is added to 331.7g purified water to make up a talc dispersion. Subsequently, 8.0g triethyl citrate (TEC) followed by 126.7g Eudragit (trade mark) RS30D (30 % w/w solids content) and 6.7g Eudragit (trade mark) RL30D (30 % w/w solids content) are added. The coating dispersion is mixed thoroughly.

Coating procedure

The drug-containing cores (500g) are dispensed into the Wurster fluid bed coater (Strea-1, Aeromatic Fielder). The coating dispersion is applied until it is depleted. When the coat application is completed, the product is dried under the same conditions for five minutes and then discharged. The following approximate size distribution, referring to diameter, is obtained: <0.71mm, 2.6% (by weight); 0.71-1.18mm, 97.3% (by weight); 1.18-1.4mm, 0.1% (by weight); >1.4mm, 0% (by weight). The particles are dusted with 28.4g talc to prevent them from sticking during the curing step. The particles are cured in a fan-assisted oven at 40 °C for 24 hours to complete the membrane-forming process and to remove excess moisture. Excess talc is removed by screening through an appropriate size mesh.

Example 2: Particulate composition containing eletriptan hemisulphate

Preparation of drug-layered core

A drug layer solution is prepared by adding 649.8g purified water to a container equipped with a mixer. With vigorous mixing, 27.1g hydroxypropyl methylcellulose (Methocel E50LV), 2.7g polyethylene glycol (PEG 400) and 135.4g eletriptan hemisulphate are dissolved therein. Mixing is continued until complete dissolution is achieved. Finally 433.2g ethanol is added and the solution is mixed thoroughly.

Non-pareil seeds (134.8g, 18/20 mesh, Nu-Pareil) are dispensed into a Wurster fluid bed coater (Strea-1, Aeromatic Fielder). After fluidisation of the non-pareils, spraying of the drug layer solution is commenced to layer drug solution effectively onto the seeds. Spraying is continued until the drug layer solution is exhausted. The beads are dried under the same conditions for 15 minutes. The beads have the following approximate size distribution, referring to their diameter: <1.18mm, 9.9% (by weight); 0.18-1.4mm, 70.5% (by weight); 1.4-1.7mm, 14.6% (by weight); >1.7mm, 5% (by weight). The 0.18-1.4mm fraction is used in the subsequent coating step.

Preparation of coating dispersion

A coating dispersion is made in the following manner. In a container equipped with a mixer, 15.0g talc is added to 195.0g purified water to make up a talc dispersion. Subsequently, 6.0g triethyl citrate (TEC) followed by 95.0g Eudragit (trade mark) RS30D (30 % w/w solids content) and 5.0g Eudragit (trade mark) RL30D (30 % w/w solids content) are added. The coating dispersion is mixed thoroughly.

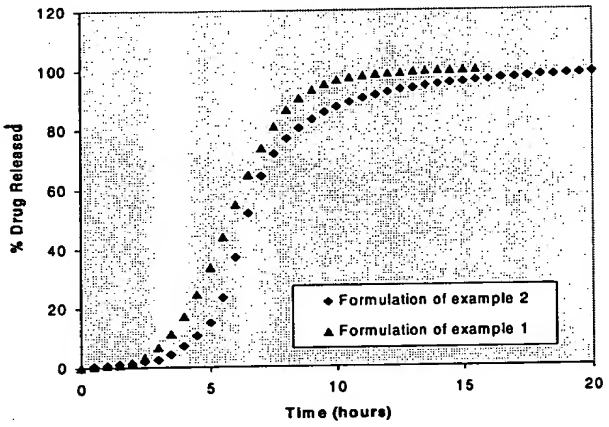
Coating procedure

The drug-containing cores (200g) are dispensed into a Wurster film coater (Strea-1, Aeromatic Fielder). The coating dispersion is applied until it is depleted. When the coat application is completed, the product is dried under the same conditions for five minutes and then discharged. The particles so obtained have the following approximate size distribution, referring to their diameter: <1.18mm, 8% (by weight); 1.18-1.4mm, 56% (by weight); 1.4-1.7mm, 30% (by weight); >1.7mm, 6% (by weight). The particles are dusted with 12.5g talc to prevent them from sticking during curing. The particles are cured in a fan-assisted oven at 40 °C for 24 hours to complete the membrane formation process and to remove excess moisture. Excess talc is removed by screening using an appropriate size mesh.

Example 3: Determination of the drug release profiles of Examples 1 and 2

Sigmoidal controlled drug release is illustrated by the following graph which plots the rate of release of eletriptan hydrobromide and eletriptan hemisulphate from separate particulate compositions of the present invention into water buffered to pH 7.5 (see the European Pharmacopeia) containing 0.1 mol/l of sodium chloride. The particulate compositions used are the two formulations described in Examples 1 and 2 respectively. A dissolution type 1

apparatus with baskets was used according to USP XXIII at 100 rpm and 37 °C.



For the formulation of Example 1, the lag time during which up to 5% by weight of the drug was released was about 2.5 hours, 50% by weight of the drug was released by about 5.75 hours and 95% by weight of the drug was released by about 10 hours. For the formulation of Example 2, the lag time during which up to 5% by weight of the drug was release was about 3.5 hours, 50% by weight of the drug was released by about 6.5 hours and 95% by weight of the drug was released by about 14.5 hours.

CLAIMS

1. A pharmaceutical composition in particulate form, suitable for oral administration, including a core containing eletriptan or a pharmaceutically acceptable salt thereof, the core being coated with a water-insoluble, permeable coating including one or more acrylic copolymer(s) containing trimethylammoniumethylmethacrylate groups, said composition being capable of achieving a sigmoidal pattern of controlled drug release.

2. A composition, as claimed in claim 1, wherein the core contains eletriptan hydrobromide.

3. A composition, as claimed in claim 1, wherein the core contains eletriptan hemisulphate.

4. A composition, as claimed in any preceding claim, wherein the core is formed as a particle of eletriptan, or a pharmaceutically acceptable salt thereof, and optionally one or more extrusion aid(s), binder(s) or diluent(s).

5. A composition, as claimed in any one of claims 1 to 3, wherein the core is formed as a layer of eletriptan, or a pharmaceutically acceptable salt thereof, and a binder on the surface of a seed.

6. A composition, as claimed in any preceding claim, wherein the core has a diameter of from 0.2 to 2mm.

7. A composition, as claimed in claim 6, wherein the core has a diameter of from 0.5 to 1.4mm.

8. A composition, as claimed in any preceding claim, wherein the core contains from 10 to 90% w/w of eletriptan.

9. A composition as claimed in claim 8, wherein the core contains from 20 to 60% w/w of eletriptan.

10. A composition, as claimed in any one of claims 1 or 2, wherein the core comprises eletriptan hydrobromide, microcrystalline cellulose and lactose.

11. A composition, as claimed in any one of claims 1 or 3, wherein the core comprises eletriptan hemisulphate, hydroxypropylmethylcellulose, polyethylene glycol and a non-pareil seed.

12. A composition, as claimed in any preceding claim, wherein an additional protective layer is inserted between the core and the water-insoluble, permeable coating.

13. A composition, as claimed in any preceding claim, wherein the acrylic copolymer(s) containing trimethylammoniumethylmethacrylate groups is/are selected from Eudragit RL (Trade Mark) and Eudragit RS (Trade Mark).

14. A composition, as claimed in claim 13, wherein a mixture of copolymers comprising 95:5, by weight, Eudragit RS (Trade Mark):Eudragit RL (Trade Mark) is used.

15. A composition, as claimed in any preceding claim, wherein the water-insoluble, permeable coating has a thickness of from 10 to 100 microns.

16. A composition, as claimed in claim 15, wherein the water-insoluble, permeable coating has a thickness of from 20 to 50 microns.

17. A composition, as claimed in claim 15, wherein the water-insoluble, permeable coating has a thickness of from 40 to 80 microns.

18. A composition, as claimed in any preceding claim, wherein the water-insoluble, permeable coating includes Eudragit RL (Trade Mark), Eudragit RS (Trade Mark), talc and triethyl citrate.

19. A pharmaceutical composition including eletriptan or a pharmaceutically acceptable salt thereof and at least one other pharmaceutically acceptable component which is capable of delivering eletriptan, or a pharmaceutically acceptable salt thereof, into an aqueous solution buffered at pH 7.5 with a sigmoidal controlled release profile wherein (a) 5% by weight of the drug is released at a time point from 1.5 to 7 hours following addition, (b) 50% by weight of the drug is released at a time point from 4 to 11 hours following addition and (c) 95% by weight of the drug is released at a time point from 6.5 to 20 hours following addition.

20. A pharmaceutical formulation including a composition, as defined in any preceding claim, and one or more pharmaceutically acceptable excipient(s), diluent(s) or carrier(s).

21. A pharmaceutical formulation, as claimed in claim 20, which is a hard gelatine capsule.

22. A dual release formulation which includes a particulate sigmoidal controlled release composition, as claimed in any one of claims 1 to 19, in combination with an immediate release composition of eletriptan, or a pharmaceutically acceptable salt thereof.

23. A dual release formulation as claimed in claim 22 wherein the immediate release composition of eletriptan includes eletriptan, or a pharmaceutically acceptable salt thereof and sodium cross-linked carboxymethyl cellulose.

24. A composition as claimed in any one of claims 1 to 19 or a formulation as claimed in any one of claims 20 to 23 for use as a medicament.

25. The use of a composition as claimed in any one of claims 1 to 19 or a formulation as claimed in any one of claims 20 to 23 in the manufacture of a medicament for the treatment of a disease for which a 5-$HT_{1B/1D}$ receptor agonist is indicated.

26. The use of a composition as claimed in any one of claims 1 to 19 or a formulation as claimed in any one of claims 20 to 23 in the manufacture of a medicament for (a) the treatment of migraine or (b) the prevention of migraine recurrence.

27. The use of dual release formulation as claimed in any one of claims 22 to 23 in the manufacture of a medicament for the treatment of migraine and the prevention of migraine recurrence.

28. A method of treatment of a disease for which a 5-$HT_{1B/1D}$ receptor agonist is indicated in a mammal, including a human, comprising administration to said mammal a therapeutically effective amount of a composition as claimed in any one of claims 1 to 19 or a formulation as claimed in any one of claims 20 to 23.

29. A method of (a) treatment of migraine or (b) prevention of migraine recurrence in a mammal, including a human, comprising administration to said mammal of a therapeutically effective amount of a composition as claimed in any one of claims 1 to 19 or a formulation as claimed in any one of claims 20 to 23.

30. A method of treatment of migraine and prevention of migraine recurrence in a mammal, including a human, comprising administration to said mammal of an effective amount of a dual release formulation as claimed in any one of claims 22 to 23.

31. A sigmoidal controlled release pharmaceutical composition containing eletriptan or a pharmaceutically acceptable salt thereof.

32. A process for the preparation of a particulate composition, as claimed in claim 1 or 2, comprising (a) forming a core containing eletriptan, or a pharmaceutically acceptable salt thereof and (b) coating the core with a water-insoluble, permeable coating comprising one or more acrylic copolymer(s) containing trimethylammoniumethylmethacrylate groups.

33. A process for the preparation of a particulate composition, as claimed in claim 1 or 3, comprising (a) forming a core by layering eletriptan, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable binder onto the surface of a pharmaceutically acceptable seed and (b) coating the core with a water-insoluble, permeable coating comprising one or more acrylic copolymer(s) containing trimethylammoniumethylmethacrylate groups.